

I. AMENDMENT

Prior to further action on the merits, please amend the application as follows.

IN THE SPECIFICATION

Please delete the Sequence Listing presently of record in the application (pages 1 through 37) and substitute therefor new pages 1 through 39, enclosed herewith, which comprise a substitute Sequence Listing.

Please replace the paragraph at page 5, lines 20-21 with the following rewritten paragraph:

B1
~~Hence the present invention makes available a process for the production of a mistletoe lectin polypeptide or a fragment thereof in the heterologous system having the following sequence (SEQ ID NO: 1).~~

Please replace the paragraph at page 7, at lines 5-7 with the following rewritten paragraph:

B2
~~Analogously to this process, two further production processes for the mistletoe lectin A-chain (MLA) (SEQ ID NO: 2) and mistletoe lectin B-chain (MLB) (SEQ ID NO: 3) are made available, which contain the following sequences or a fragment thereof.~~

Please replace the paragraph at page 8, line 15-16 with the following rewritten paragraph:

B3
~~Furthermore, a mistletoe lectin polypeptide or a fragment thereof, which includes the sequence variability of the various MLA and MLB chains, having the following sequence is provided (SEQ ID NO: 1).~~

Please replace the paragraph at page 10, at lines 3-5 with the following rewritten paragraph:

B4
~~Apart from this, mistletoe lectin polypeptides of the mistletoe lectin A-chain (SEQ ID NO: 2) and mistletoe lectin B-chain (SEQ ID NO: 3) or fragments of these sequences are provided, which include the following sequences:~~

Please replace the paragraph at page 11, beginning at line 17 with the following rewritten paragraph:

B5
The sequence which includes the above-described variability of the ML-I polypeptides occurring in mistletoe cells is shown in Figure 1b (SEQ ID NO: 4). A specific sequence for MLA2 of mistletoe lectin I, which was likewise produced according to the process presented above, is shown in Figure 3b (SEQ ID NO: 38). Figures 7b to 12b (SEQ ID NOS: 6-11) include specific mistletoe lectin B-chain sequences, which were likewise produced according to the process described above.

Please replace the paragraph at page 12, line 5- 7 with the following rewritten paragraph:

B6
b) amplifying mistletoe cell RNA or chromosomal mistletoe lectin DNA by PCR using oligonucleotides which are derived from the mistletoe lectin polypeptide shown in Fig. 1b (SEQ ID NO: 4), and

Please replace at page 12, line 23 with the following rewritten line:

B7
GTN MGN GAY GAY GAY TTY CA (SEQ ID NO:33)

Please replace at page 12, line 25 with the following rewritten line:

B8
AT YTG RTT NGG YTT NCC NGT (SEQ ID NO: 34)

Please replace the paragraph at page 13, lines 3-5 with the following rewritten paragraph:

B9. In a further reaction step, using specific oligonucleotides, the 5'- and 3'-lying sequences of the first amplification product were determined by means of the RACE technique (Example 3). The oligonucleotide used for the 5'-RACE reaction has the following sequence (SEQ ID NO: 35):

Please replace at page 13, line 7 with the following rewritten line:

B10. The oligonucleotide used for the 3'-RACE reaction has the following sequence (SEQ ID NO: 36):

Please replace at page 13, lines 20-22 with the following rewritten line:

B11. Nucleic acid molecules which are made available by this process and code for a polypeptide as described above, include the following sequences for ML-I (SEQ ID NO: 12), MLA (SEQ ID NO: 13) and MLB (SEQ ID NO: 14) or fragments thereof:

Please replace the paragraph at page 16, beginning at line 18 with the following rewritten paragraph:

B12. A specific nucleic acid molecule which was prepared by the process stated above and includes the entire ML-I coding sequence, is shown in Figure 1a (SEQ ID NO: 15). Further specific nucleic acid molecules, which code for the MLA chain of mistletoe lectin I and were prepared by the process stated above, are shown in Figure 2a (SEQ ID NO: 16) and Figure 2b (SEQ ID NO: 37). Specific sequences for MLB nucleic acid molecules, which were prepared by the process described above, are listed in Figures 7a to 12a (SEQ ID NOS: 21-26). Here, each of these nucleic acid sequences codes for a polypeptide which emerged by protein sequencing of the ML-I mixture from natural mistletoe extract.

Please replace the paragraph at page 17, beginning at line 3 with the following rewritten paragraph:

B13 In addition, the present invention includes nucleic acid molecules which code for a mistletoe lectin polypeptide, as described above, and are characterized in that the codon usage is matched to the requirements of a heterologous host. Figure 4a (SEQ ID NO: 18) shows such a nucleic acid sequence, wherein the codon usage is matched to the preferred codon usage of the genus *Brassica*. This genus was chosen, since both as the Summer and also as the Winter form it thrives outstandingly in the middle latitudes of Europe, North America and Asia. The possible uses of rape for the production of recombinant proteins have been demonstrated by various firms and research institutes. Examples, of its use are the production of gastric lipase for use in the treatment of cystic fibrosis or coupling to oleosins for greater ease of purification of the recombinant proteins from the lipid phase of the rape oil seeds.

Please replace the paragraph at page 17, beginning at line 13 with the following rewritten paragraph:

B14 The sequences shown in Figures 5a (SEQ ID NO: 19), 6a (SEQ ID NO: 20), and 13a to 18a (SEQ ID NOS: 27-32) represent nucleic acid molecules which code for MLA polypeptides or for MLB polypeptides of mistletoe lectin I and whose codon usage is likewise matched to the genus *Brassica*. The degree of homology between these matched sequences to the nucleic acid sequences shown in Figs 2a (SEQ ID NO: 16) and 7a (SEQ ID NO: 21) is ca. 61% for MLA and about 63% for MLB.

Please replace at page 20, lines 27-29 with the following rewritten paragraph:

B15 ~~Furthermore, the present invention also includes a process for the production of a mistletoe lectin polypeptide in mistletoe cells and/or transgenic mistletoe plants having the following sequence (SEQ ID NO: 1):~~

Please replace at page 22, at lines 20-22 with the following rewritten paragraph:

B16
USCIS
~~On the basis of the process described above, two further production processes for the~~
mistletoe lectin A-chain (SEQ ID NO: 2) and mistletoe lectin B-chain (SEQ ID NO: 3) or
a fragment thereof are provided, which contain the following sequences or a fragment
thereof:

Please replace at page 24, line 9-11 with the following rewritten lines:

- B17
- b) amplifying mistletoe cell RNA or chromosomal mistletoe lectin DNA by PCR using oligonucleotides which are derived from the mistletoe lectin polypeptide shown in Fig. 1b (SEQ ID NO: 4), and

Please replace the paragraph at page 24, beginning at line 20 with the following rewritten paragraph:

B18

Firstly, plant RNA or DNA is isolated preferably from fresh material by various generally known processes (Quiagen experimental protocol, Nickrent D L et al., American Journal of Botany, vol. 81, No. 9 (1994): 1149-1160; Example 1). Using the degenerate oligonucleotides BI and BII described in Example 1, which are derived from the mistletoe lectin polypeptide shown in Figure 1b (SEQ ID NO: 4), the mistletoe lectin-I gene is amplified in a PCR reaction, the conditions for which are set out in Example 2. If this amplification step does not include the complete open reading frame of ML-I, the 5' and 3' region of the amplified nucleic acids can be identified using the RACE technique with the respective oligonucleotides stated in Example 3. The nucleic acid molecules thus obtained are isolated and if necessary ligated into a vector using suitable restriction cleavage sites in such a way that this contains the complete open reading frame. A nucleic acid molecule or a fragment thereof contained in this vector, which codes for a polypeptide such as described above in a mistletoe cell or a transgenic mistletoe plant, comprises the following sequence (SEQ ID NO: 12):

Please replace at page 26, at lines 15-17 with the following rewritten lines:

B19

A nucleic acid molecule according to the invention or a fragment thereof, which codes for one of the above-mentioned MLA polypeptides in a mistletoe cell or a transgenic mistletoe plant, comprises the following sequence (SEQ ID NO: 13):

Please replace at page 27, at line 13 with the following rewritten line:

B20

Furthermore, a nucleic acid molecule or a fragment thereof, which codes for one of the above-mentioned MLB polypeptides in a mistletoe cell or a transgenic mistletoe plant, having the following sequence is made available (SEQ ID NO: 14):

Please replace at page 28, line 18 with the following rewritten line:

B21

A specific nucleic acid molecule which is to be expressed in a mistletoe cell or in a transgenic mistletoe plant and codes for ML-I, is shown in Figure 1a (SEQ ID NO: 15). Further specific nucleic acid plants, which are modified in their codon usage in such a manner that as a result the expression rate is optimized.

Please replace the paragraph at page 29, beginning at line 14 with the following rewritten paragraph:

B22

The following figures and examples illustrate the invention:

Fig. A: Representation of a mistletoe lectin-I dimer;

Fig. 1: Representation of the (a) nucleic acid sequence (SEQ ID NO: 15) and (b) amino acid sequence (SEQ ID NO: 4) of MLA-I;

Fig. 2: Representation of the (a) nucleic acid sequence (SEQ ID NO: 16) and (b) amino acid sequence (SEQ ID NO: 37) of mistletoe lectin A1;

Fig. 3: Representation of the (a) nucleic acid sequence (SEQ ID NO: 17) and (b) amino acid sequence (SEQ ID NO: 38) of mistletoe lectin A2;

Fig. 4: Representation of (a) the nucleic acid sequence of MLI (SEQ ID NO: 18); wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin I (matched) (SEQ ID NO: 4);

Fig. 5: Representation of the nucleic acid sequence of mistletoe lectin A1 (SEQ ID NO: 19), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin A1 (matched) (SEQ ID NO:39);

Fig. 6: Representation of (a) the nucleic acid sequence of mistletoe lectin A2 (SEQ ID NO: 20), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin A2 (matched) (SEQ ID NO: 5);

Fig. 7: Representation of the (a) nucleic acid sequence (SEQ ID NO: 21) and (b) amino acid sequence (SEQ ID NO: 6) of mistletoe lectin B;

Fig. 8: Representation of the (a) nucleic acid sequence (SEQ ID NO: 22) and (b) amino acid sequence (SEQ ID NO: 7) of mistletoe lectin B1;

Fig. 9: Representation of the (a) nucleic acid sequence (SEQ ID NO:23) and (b) amino acid sequence (SEQ ID NO: 8) of mistletoe lectin B2;

Fig. 10: Representation of the (a) nucleic acid sequence (SEQ ID NO:24) and (b) amino acid sequence (SEQ ID NO: 9) of mistletoe lectin B3;

Fig. 11: Representation of the (a) nucleic acid sequence (SEQ ID NO:25) and (b) amino acid sequence (SEQ ID NO: 10) of mistletoe lectin B4;

Fig. 12: Representation of the (a) nucleic acid sequence (SEQ ID NO:26) and (b) amino acid sequence (SEQ ID NO: 11) of mistletoe lectin B5;

Fig. 13: Representation of (a) the nucleic acid sequence of mistletoe lectin B (SEQ ID NO:27), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin B (matched) (SEQ ID NO: 6);

Fig. 14: Representation of (a) the nucleic acid sequence of mistletoe lectin B1 (SEQ ID NO:28), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin 1 (matched) (SEQ ID NO: 7);

Fig. 15: Representation of (a) the nucleic acid sequence of mistletoe lectin B2 (SEQ ID NO:29), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin B2 (matched) (SEQ ID NO: 8);

Fig. 16: Representation of (a) the nucleic acid sequence of mistletoe lectin B3 (SEQ ID NO:30), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin B3 (matched) (SEQ ID NO: 9);

B22
conclude
Fig. 17: Representation of (a) the nucleic acid sequence of mistletoe lectin B4 (SEQ ID NO:31), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin B4 (matched) (SEQ ID NO: 10); and,

Fig. 18: Representation of the (a) nucleic acid sequence of mistletoe lectin B5 (SEQ ID NO:32), wherein the nucleic acid sequence is matched to the codon usage of *Brassica* and (b) the amino acid sequence of mistletoe lectin B5 (SEQ ID NO: 11).

Please replace at page 31, line 12 with the following rewritten line:

B23
B1. GTN MGN GAY GAY GAY TTY CA (SEQ ID NO: 33)

Please replace at page 31, line 13 with the following rewritten line:

B24
B2. AT YTG RTT NGG YTT NCC NGT (SEQ ID NO: 34)

Please replace at page 32, line 3 with the following rewritten line:

B25
CAC AGC AGT ATT ACA GTC GAA (SEQ ID NO: 35)

Please replace at page 32, line 4 with the following rewritten line:

29
GTC TAT GTG ATG ATC TTC GAC TGT (SEQ ID NO: 36).

IN THE CLAIMS

Please cancel claims 1-45 as amended by Preliminary Amendment, without prejudice.

Please add following new claims 46-90 :